Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products
Advisory Committee Meeting
Briefing Package

For

NDA 21-414
Vitrase (ovine hyaluronidase for intravitreal administration)

Sponsor:

ISTA Pharmaceuticals
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Draft Advisory Committee Meeting Questions:

Are additional analyses of the data needed to understand the safety or efficacy of Vitrase for the treatment of vitreous hemorrhage?

Are additional studies needed to establish the efficacy of this product?

Has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage?

Is there a concern about the death rate observed in these studies?

What additional clinical studies would be helpful in further evaluating the potential benefits of Vitrase therapy?

Are there adverse experiences that are of particular concern for this product?

Does the committee recommend approval of Vitrase for the treatment of vitreous hemorrhage?

Clinical Background

Vitreous hemorrhage is an important cause of painless sudden vision loss. It is typically associated with older adults and severe ocular conditions. The presence of systemic diseases such as diabetes mellitus is an important contributory cause in many cases of vitreous hemorrhage. Some of the more common causes of vitreous hemorrhages are proliferative diabetic retinopathy, posterior vitreous detachment, trauma, branch or central retinal vein occlusion and proliferative sickle cell retinopathy.

The most common complications associated with vitreous hemorrhage are diminished visual acuity due to the obscuration caused by the blood and obstruction of visualization of the posterior pole which may cause delay in the diagnosis of underlying retinal pathology. Other complications associated with vitreous hemorrhage are ghost cell glaucoma and hemosiderosis bulbi which may result in retinal damage. Therapies to treat vitreous hemorrhage are important since they should result in a shortened duration of visual impairment and potentially result in earlier diagnosis which may avert further complications.

Current options available for the management of vitreous hemorrhage are vitrectomy surgery and observation. Many physicians wait at least 6 months or longer before instituting vitrectomy to allow for spontaneous clearing. The outcome of vitrectomy surgery varies greatly depending on the length of non-clearing hemorrhage and the underlying etiology. Some of the complications associated with vitrectomy are retinal breaks, rhegmatogenous retinal detachment, elevated intraocular pressure and progressive cataract.

Hyaluronidase is a non-surgical treatment to manage vitreous hemorrhage. The mechanism of action is thought to be the ability of hyaluronidase to liquefy vitreous. Liquefaction of the vitreous is thought to increase the diffusion rate of erythrocytes and phagocytes through the vitreous and facilitates red cell lysis and phagocytosis. Improvement of vitreous hemorrhage density and/or clearance of vitreous hemorrhage should allow better visual acuity and better visualization of the retina for diagnosis of retinal pathology and further treatment (if needed).

Foreign Marketing

The active ingredient in Vitrase is highly purified ovine testicular hyaluronidase. Marketing approval for Vitrase for ophthalmic intravitreal injection was granted in Mexico on November 13, 1998, but the product has not been marketed there. To date, no other marketing applications for Vitrase have been submitted.

Highly purified bovine testicular hyaluronidase has been the active ingredient in drug products (e.g., Wydase) marketed by other sponsors for different indications and routes of administration than those proposed by ISTA for Vitrase.

Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Table 1 - Quantitative Composition of Vitrase

Ingredient	Amount/vial
Hyaluronidase	6000 IU (7440 USP units)
Potassium Phosphate Monobasic, NF	1.22 mg
Potassium Phosphate Diabasic, USP	1.92 mg
Lactose Monohydrate, NF	5 mg

*Amount of hyaluronidase manufacturing for 08961X manufactured at Prima Pharm. The pivotal clinical studies and most of the GLP studies used 08961X lots that were manufactured with a . The hyaluronidase formulation for commercial lots will be .

Table 2 –(Complete Table Redacted)

**The USP<85> kinetic-turbidimetric method is performed at release while the USP<85> kinetic chromogenic method is performed in stability.
***Dose calculated as 0.050mL injection volume of a 5.4mL reconstitution of the vial contents (0.93% of the vial contents.)

The proposed particular matter specification is not consistent with other ophthalmic products approved after 1988. The Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products will expect the proposed product tests and specifications to be modified so that they are consistent with other ophthalmic drug products.

Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Table 1 - Quantitative Composition of Vitrase

Ingredient	Amount/vial
Hyaluronidase	6000 IU (7440 USP units) 12.5% overage*
Potassium Phosphate Monobasic, NF	1.22 mg
Potassium Phosphate Diabasic, USP	1.92 mg
Lactose Monohydrate, NF	5 mg

*Amount of hyaluronidase manufacturing overage for 08961X manufactured at Prima Pharm. The pivotal clinical studies and most of the GLP studies used 08961X lots that were manufactured with a 12.5% overage. The hyaluronidase formulation overage for commercial lots will be 8.9%

Table 2 – Proposed Product Tests and Specifications

Test	Method	Release Specification	Shelf-Life Specification
pH, constituted solution in saline TS	AP-001	6.4-6.9 (in saline TS)	6.4-6.9 (in saline TS)
Physical appearance of lyophilized powder	AP-001	White fluffy cake or powder free from visible evidence of contamination	White fluffy cake or powder free from visible evidence of contamination
Physical appearance, constituted solution in saline TS	AP-001	Solution is clear and colorless	Solution is clear and colorless
Water content	AP-014	≤5%	≤5%
Osmolarity	USP<785>**	290-310- mOsM	Performed at release only
Hyaluronidase activity	AP-012	$6.46x10^3$ – $8.54x10^3$ USP units/vial	$5.6x10^3$ – $8.54x10^3$ USP units/vial
Hyaluronidase activity of reconstituted solution* (5.4 ml, 6-hr test)	AP-012	$1.20x10^3$ – $8.54x10^3$ USP Units/ml	$1.04x10^3$ – $1.58x10^3$ USP Units/ml
Reconstitution time	AP-001	<15 seconds	Performed at release only
Total protein	AP-009	0.38-0.57 mg protein/vial	0.38-0.57 mg protein/vial
Hyaluronidase content	AP-013	≥0.10 mg/mg protein	≥0.10 mg/mg protein
Protein shift by SDS-PAGE	AP-011	≤0.23 kDa (change in mobility compared to control)	≤0.23 kDa (change in mobility compared to control)
Lactose	WCAS SOP-4240	4.5-5.5 mg per vial	Performed at release only
Phosphate	WCAS SOP-4320	1.7-2.2 mg per vial	Performed at release only
Particulate matter in reconstituted solution	USP<788> HIAC	≤ 6000 particles ≥10 um ≤ 600 particles ≥ 25 um	≤ 6000 particles ≥10 um ≤ 600 particles ≥ 25 um
Bacterial endotoxins	USP<85>**	≤ 0.3 EU/dose***	≤ 0.3 EU/dose***
Sterility	USP<71> membrane filtration	sterile	sterile

*Tested immediately after reconstitution and then after storage at 25°C for 6 hours ±15 minutes. At the 6-hr time point, the measurements will include hyaluronidase activity, pH, color and clarity of solution.
**The USP<85> kinetic-turbidimetric method is performed at release while the USP<85> kinetic chromogenic method is performed in stability.
***Dose calculated as 0.050mL injection volume of a 5.4mL reconstitution of the vial contents (0.93% of the vial contents.)

The proposed particular matter specification is not consistent with other ophthalmic products approved after 1988. The Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products will expect the proposed product tests and specifications to be modified so that they are consistent with other ophthalmic drug products.

IV. Description of Clinical Data Sources

Protocol	Study Design	Treatment Groups	Number of Patients	Dosing/ Duration	Age, Sex, Race
VIT-02-08961X Phase III **Participating Sites** Canada: 9 centers Mexico: 3 centers U.S.: 61 centers	**Multicenter double-masked randomized 4-arm, placebo controlled, parallel group** First patient randomized in Watchful Waiting Control Protocol 19 November 1998 First patient randomized in saline control Protocol 9 April 1999	Test Product Ovine hyaluronidase 08961X/224C: 7.5IU 55IU 75IU **Control** Saline	**Saline Control Protocol:** 7.5IU: 180 55IU: 175 75IU: 194 Saline: 191 **Watchful Waiting Control Protocol:** No injection: 18 7.5IU 18 55IU: 18 75IU: 17	Single intravitreous injection, study visits at Day 1, Week 1, Months 1,2,3,6, and then every six months thereafter	Mean age **61.9 (25 to 97)** **Sex** Male 52% Female 48% **Race** Caucasian 51% African-American 6% Asian/Pacific island 4% Other:40%
VIT-03-08961X Phase III **Participating Sites** Australia: 8 centers Brazil: 6 centers Hungary: 6 centers Italy: 4 centers Netherlands: 4 centers Poland: 10 centers South Africa: 10 centers Spain: 4 centers U.K.: 12 centers	**Multicenter double-masked randomized 3-arm, placebo controlled, parallel group** First patient randomized 01 June 1999	Test Product Ovine hyaluronidase 08961X/224C: 55IU 75IU **Control** Saline	55IU: 184 75IU: 180 Saline: 187	Single intravitreous injection, study visits at Day 1, Week 1, Months 1,2,3,6, and then every six months thereafter	Mean age **61.9 (23 to 93)** **Sex** Male 50% Female 50% **Race** Caucasian 84% African-American 10% Asian/Pacific island 4% Other:3%
VIT-01-VIT-08961X Phase III **Participating Sites** Singapore	Double-masked randomized 2-arm, placebo controlled, parallel group	Test Product Ovine hyaluronidase 08961X/224B&224C: 75IU **Control** Saline	75IU: 31 Saline: 30	Single intravitreous injection, 12 month follow-up	Mean age **57.5 (22 to 76)** **Sex** Male 51% Female 49% **Race** Asian/Pacific island 100%

[a] active drug administered in the morning and evening with masked vehicle administered in the afternoon

Clinical Review Methods

Two phase 3 studies for Vitrase were reviewed in this application. The doses that these two studies had in common were 55IU and 75IU. Based on evaluation of the data, the sponsor has submitted this new drug application to support the used of the 55IU intravitreal dose of Vitrase for the treatment of vitreous hemorrhage.

A non–IND controlled study of Vitrase for vitreous hemorrhage clearance (conducted in Singapore as a Phase 3 marketing application study) was excluded from this review. The study was terminated early by ISTA. It did not use similar methodology for visual acuity assessment that could be converted to LogMAR units for comparison with other studies, and it used a smaller injection volume (30ul) than was given in the other clinical studies (50ul).

Efficacy Results

Study 1 - Protocol VIT-02-08961X

Title: Phase III Safety and Efficacy Study of Vitrase (ovine hyaluronidase) for Ophthalmic Intravitreous Injection for clearance of Severe Vitreous Hemorrhage

Objective: The primary objective of this study was to evaluate the safety and efficacy of a single intravitreous injection of 50ul of Vitrase (hyaluronidase) 7.5 IU, 55 IU, or 75 IU (equivalent to 9.3, 68, and 93 USP units) compared with 0.9% sodium chloride injection USP (saline solution) for the treatment of vitreous hemorrhage.

Study Design: This was a four-arm, double-masked, prospective, randomized, parallel-group study. Patients were followed for a minimum of 12 months post-randomization and every six months thereafter. During the first 12 months, study visits were scheduled at 1 day, 1 week, and 1, 2, 3, 6, and 12 months post treatment.

This study was conducted in two parts: an initial open-label study using Watchful Waiting as the control and a subsequent protocol with a Saline Control arm. For the Saline Control Protocol a sample size of 680 patients (170 per treatment group) was planned. The intent-to-treat population for the Saline Control Protocol included 750 patients: 193 in the saline control group, 181 in 7.5 IU, 179 in 55 IU, and 197 in 75 IU Vitrase treatment groups. Seven hundred and forty (740) patients were included in the safety population. Seventy-two patients were randomly assigned to a treatment group in the Watchful Waiting Control Protocol.

Test Drug Schedule: Single intravitreous injection was administered in the study eye.

Table 3 - Clinical Sites – Study VIT-02-08961X

Site No.	Principal Investigator	Center / Address	Watchful Waiting Control Patients	Saline Control Patients Randomized	Total Patients Randomized
148-1	Antoszyk, Dr. Andrew	Charlotte, NC 28204	0	4	4
132-1	Avery, Dr. Robert	Santa Barbara, CA 93103	0	7	7
117-1	Bertolucci, Dr. George	Fresno, CA 93721	0	2	2
181-1	Bhavsar, Dr. Abdhish	Minneapolis, MN 55404	0	6	6
116-1	Bradford, Dr. Reagan	Oklahoma, OK 73104	2	14	16
185-1	Brownlow, Dr. Robert	Roanoke, VA 24008	0	1	1
138-1	Brucker, Dr. Alexander (Ho, Dr. Allen)[a]	Philadelphia, PA 19104	0	5	5
109-1	Carim, Dr. Moiz	Wyomissing, PA 19610	5	12	17
149-1	Castillejos, Dr. Maria	Chula Vista, CA 91910	0	15	15
113-1	Chan, Dr. Clement K.	Palm Springs, CA 92262	1	10	11
183-1	Chaudhry, Dr. Nauman	Hamden, CT 06518	0	1	1
142-1	Connor, Dr. Thomas B.	Milwaukee, WI 53226	0	2	2
110-1	Davidorf, Dr. Frederick	Columbus, OH 43210	3	8	11
129-1	Dayan, Dr. Alan R. (Farrell, Dr. Gault)[a]	Colorado Springs, CO 80909	1	3	4
158-1	Deschenes, Dr. Jean	Montreal, Quebec H3A 1A1	0	6	6
170-1	Devenyi, Dr. Robert	Toronto, Ontario M2P 1E3	0	52	52
184-1	Dickinson, Dr. John	Halifax, Nova Scotia B3H 2Y9	0	3	3
162-1	Dyer, Dr. David	Kansas City, MO 64151	0	4	4
154-1	Eaton, Dr. Alexander	Fort Myers, FL 33901	0	11	11
188-1	Engstrom, Dr. Robert	Sylmar, CA 91342	0	11	11
167-1	Erasmus, Dr. Murray	Saskatoon, Saskatchewan S7K 0M7	0	37	37
133-1	Feldman, Dr. Robert	Altamonte Springs, FL 32701	3	0	3
171-1	Fox, Dr. Gregory	Kansas City, MO 64111	0	7	7
139-1	Garcia, Dr. Charles	Houston, TX 77002	0	5	5
178-1	Garcia-Salinas, Dr. Raul	Regina, Saskatchewan S4T 1A5	0	3	3
130-1	Gitter, Dr. Kurt	New Orleans, LA 70115	0	15	15
177-1	Glazer, Dr. Louis	Grand Rapids, MI 49525	0	2	2
186-1	Gonder, Dr. John	London, Ontario N6A 4G5	0	5	5

Site No.	Principal Investigator	Center / Address	Watchful Waiting Control Patients	Saline Control Patients Randomized	Total Patients Randomized
135-1	Gonzalez, Dr. Victor	McAllen, TX 78503	4	37	41
134-1	Griggs, Dr. Paul	Seattle, WA 98101	0	4	4
157-1	Gunn, Dr. Joseph	Knoxville, TN 37920	0	18	18
157-2		Kingsport, TN 37660			
157-3		Chattanooga, TN 37403			
157-4		Knoxville, TN 37922			
157-5		Johnson City, TN 37604			
176-1	Hampton, Dr. Robert	Syracuse, NY 13224	0	6	6
122-1	Holekamp, Dr. Nancy	St Louis, MO 63110	4	4	8
107-1	Holz, Dr. Eric	Houston, TX 77030	9	25	34
119-1	Hudson, Dr. Henry	Tucson, AZ 85704	0	4	4
179-1	Kaiser, Dr. Peter	Cleveland, OH 44195	0	2	2
128-1	Kaye, Dr. David	Fresno, CA 93710	0	1	1
182-1	Kertes, Dr. Peter	Ottawa, ON K1H 8L6	0	3	3
103-1	Keyser, Dr. Bruce	Lakewood, NJ 08701	4	10	14
103-2	Keyser, Dr. Bruce	New Brunswick, NJ 08901			
155-1	Kokame, Dr. Gregg	Aiea, HI 96701	0	10	10
126-1	Kuppermann, Dr. Barry	Irvine, CA 92697-4375	4	17	21
115-1	Lashkari, Dr. Kameran	Boston, MA 02114	1	7	8
111-1	Lazarus, Dr. Howard	New Albany, IN 47150	1	8	9
131-1	Lee, Dr. King	Shawnee Mission, KS 66216	1	1	2
163-1	Levine, Dr. Arthur William	Mexico DF 04030	0	40	40
187-1	Lieberman, Dr. Ronni	New York, NY 10021	0	7	7
180-1	Ma, Dr. Patrick	Vancouver BC V5Z 3N9	0	16	16
144-1	Mandava, Dr. Naresh	Denver, CO 80262	0	3	3
168-1	Mansour, Dr. Sam	San Jose, CA 95128	0	37	37
104-1	McDonald, Dr. Richard	San Francisco, CA 94109	2	14	16
145-1	Merrill, Dr. Pauline	Chicago, IL 60612	0	15	15
164-1	Morales, Dr. Virgilio	Coyacan 04030, Mexico DF	0	43	43

Site No.	Principal Investigator	Center / Address	Watchful Waiting Control Patients	Saline Control Patients Randomized	Total Patients Randomized
106-1	Orellana, Dr. Juan	Raleigh, NC 27607	1	9	10
124-1	Pappas, Dr. Stephen	Bethesda, MD 20817	1	0	1
114-1	Patel, Dr. Arun	Sacramento, CA 95819	1	9	10
137-1	Patel, Dr. Samir	Chicago, IL 60637	1	2	3
147-1	Paul, Dr. Matthew (Sperling, Marvin)[a]	Danbury, CT 06810	0	3	3
172-1	Pautler, Dr. Scott	Tampa, FL 33614	0	7	7
102-1	Pendergast, Dr. Scott	Beechwood, OH 44122	1	0	1
136-1	Poulose, Dr. Abraham (Dr. Joseph Tauber)[a]	Prairie Village, KS 66208	0	2	2
165-1	Quiroz, Dr. Miguel Angel	Col. Obrera 06080, Mexico DF	0	31	31
127-1	Regillo, Dr. Carl	Philadelphia, PA 19107	1	6	7
160-1	Sanislo, Dr. Steven	Menlo Park, CA 94025	0	2	2
120-1	Sebag, Dr. Jerry	Huntington Beach, CA 92648	10	23	33
151-1	Seery, Dr. Christopher	Milburn, NJ 07041	0	3	3
151-2		Teaneck, NJ 07666			
169-1	Shakin, Dr. Eric	Great Neck, NY 11021	0	3	3
174-1	Sonkin, Dr. Peter	Nashville, TN 37203	0	10	10
175-1	Tardif, Dr. Yvon Maurice	Sainte Foy, Quebec G1W 1T7	0	12	12
146-1	Teske, Dr. Michael	Salt Lake City, UT 84132	0	11	11
112-1	Thomas, Dr. Edgar	Beverly Hills, CA 90211	6	25	31
143-1	Thompson, Dr. John	Baltimore, MD 21204	0	3	3
101-1	Wong, Dr. Keye	Sarasota, FL 34239	5	8	13
161-1	Zimmer-Galler, Dr. Ingrid	Baltimore, MD 21287	0	4	4
Total			**72**	**756**	**828**

[a] The names listed in parentheses are previous investigators that transferred responsibility for the study to another individual during the course of the study.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

Patients had to meet all of the following criteria at the screening visit to be eligible for enrollment in the study:

1. 18 years of age or older
2. Severe vitreous hemorrhage that obscured visualization of the fundus on indirect ophthalmoscopy such that red reflex with no retinal detail (retinal blood vessels) was visible posterior to the equator or no red reflex was visible *
3. Vitreous hemorrhage that was present at least one month by history or examination
4. Best corrected visual acuity in the study eye worse than 20/200
5. Ability to understand and sign the Informed Consent Form
6. Willingness and ability to make all study visits
7. Male; or female who met one of the following criteria: postmenopausal, had a hysterectomy or tubal ligation, was using an effective form of birth control, or was otherwise unable to bear children.

*Hemorrhage density was graded as follows:

Grade 0 (0):	Anatomical details of the retina are visible and pathology is easily treatable
Grade 1 (+1):	Retinal detail visible, some hemorrhage present but laser photocoagulation would still be possible
Grade 2 (+2):	Large retinal Vessels are visible, but central retinal detail is not visible enough to adequately place panretinal photocoagulation posterior to the equator
Grade 3 (+3):	Red reflex is visible but no central retinal detail (retinal blood vessels) is seen posterior to the equator
Grade 4 (+4):	No red reflex

Exclusion Criteria

If any of the following criteria applied, the patient was not eligible to enroll in the study. The first 8 criteria as listed below applied to the study eye only:

1. Corneal abnormalities that would have precluded fundus observation, or accurate readings with an applanation tonometer or a Tonopen
2. Ongoing ocular infection, inflammation, or history of a herpetic corneal lesion that had cleared within 1 month prior to the study
3. Current or prior retinal detachment, or retinal tears or breaks, or intraocular tumor as determined by history, clinical examination, and/or B-Scan ultrasound
4. More than one severe vitreous hemorrhage within the past six months (prior to the onset of the present hemorrhage)
5. Vitreous hemorrhage resulting from ocular trauma or a history of ocular trauma associated with the onset of the hemorrhage
6. Previous vitrectomy for any reason
7. Hemorrhage that was exclusively pre-retinal (subhyaloid)
8. Hemorrhage that was old and organized (e.g., yellow ochre in color, "chicken fat" in appearance)
9. Prior Vitrase therapy in either eye
10. No light perception (NLP) in either eye at any time (prior to or at the time of screening visit)
11. Currently participating in another research study or enrolled in another research study of an investigational drug or device within the past 30 days
12. Any known contraindications to the study medication
13. A known hypersensitivity to any ingredient in the study medication, anesthesia, or diagnostic agents used for tests pertaining to this protocol
14. History of sickle cell disease

Although the protocol did not exclude patients with a past history of ophthalmic surgery, investigators were advised in the Protocol Clarification Booklet issued in February 2001 to exercise caution when enrolling patients with a recent history of intraocular surgery performed on the study eye. A 30-day waiting period following such intervention was strongly recommended.

Study Medications

Each vial of Vitrase (formulation number 08961X, hyaluronidase lot 224C, Vitrase lots PHI-09-07 and PHJ-06-03) contained hyaluronidase 6000 IU (equivalent to 7440 USP units), 5.0 mg lactose, NF; 1.92 mg potassium phosphate dibasic, USP; and 1.22 mg potassium phosphate monobasic, NF. Vitrase was supplied in lyophilized form and was to be stored at refrigerated conditions, 2° to 8°C (36 to 46°F) prior to reconstitution in 0.9% sodium chloride injection, USP. Test agent was to be used within one hour of reconstitution. Detailed instructions for preparation and injection of the test agent were provided in the protocol.

Saline solution (0.9% sodium chloride injection, USP) was supplied in single-dose 10mL plastic vials and was to be stored at controlled room temperature, 15 to 30°C (59 to 86°F).

Study Masking

Study treatment was double-masked. Two study staff members, or at least one qualified pharmacy technician, were required for preparation of the test agent at each study site. These unmasked staff members were not involved in treating, examining, or evaluating the patients. All records related to patient randomization and drug accountability were housed separately from other study documentation in the unmasked Pharmacy Binder provided by ISTA.

For the original Watchful Waiting Control Protocol, neither the patient nor the investigator administering the study injection was masked. However, at the screening visit and at each efficacy assessment visit, a different investigator who was masked to treatment conducted these examinations.

For the interim analyses reviewed by the DSMB, an independent biostatistical group was employed (Synteract) to conduct the analyses and to present results (unmasked and in a closed-door session) to the DSMB. Statistical assessment of the adverse events, including SAEs, was presented to the DSMB at each meeting. Efficacy analysis of the surrogate success evaluation was also presented. No other efficacy data were presented in this interim analysis.

Study Design and Schedule of Assessments

Table 4 – Examination Schedule – Study VIT-02-08961X

Measurement	Visit 1 Screening	Visit 2 Randomization [a]	Visit 3 1 Day After Randomization	Visit 4 Day 7 ± 3 days	Visit 5 Day 30 ± 7 days	Visit 6 Day 60 ± 14 days	Visit 7 Day 92 ± 14 days	Visit 8 Day 180 ± 30 days	Visit 9 Day 365 ± 30 days
Randomization, administration of test agent		X							
1. Medical, ophthalmic history	X								
2. External eye examination	X	X	X	X	X	X	X	X	X
3. Ocular symptomatology	X	X	X	X	X	X	X	X	X
4. Best corrected visual acuity	X	X	X	X	X	X	X	X	X
5. Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X
6. Intraocular pressure	X	X	X	X	X	X	X	X	X
7. Fundus examination	X	X	X	X	X	X	X	X	X
8. B-Scan ultrasound[b]	X	X		X	[b]	[b]	[b]	[b]	[b]
9. Fundus photography[c]					[c]	[c]	[c]		
10. Adverse events	X	X	X	X	X	X	X	X	X
11. Concomitant medications	X	X	X	X	X	X	X	X	X

a Screening and randomization could have occurred on the same day. If they were more than 1 day apart, evaluations 2 through 8 were to be repeated.

b B-scan ultrasound was required at the screening visit and at Visit 4 (Week 1) to document the absence/presence of retinal detachment. At Months 1, 2, 3, 6, and 12, B-scan ultrasound was not required if media were not clear enough to allow adequate fundus visualization to rule out retinal tear or detachment.

c A fundus photograph was required as documentation only if the patient reached the definition of treatment success.

Efficacy Variable

The final Statistical Analysis Plan submitted to the FDA included a surrogate success evaluation for the primary efficacy endpoint. In order for this surrogate success to be accepted, a full and complete validation plan utilizing an outcome of improved visual function was required by the FDA. A validation plan was not submitted by ISTA, therefore the primary efficacy analysis was not accepted by the FDA. The surrogate success evaluation classified patients prior to data analysis as a treatment success if the vitreous hemorrhage cleared and one of the following criteria were met within the Month 3 visit window:

- laser treatment of the underlying condition was completed, or
- visualization of the retina revealed that surgery was required and was performed to correct the underlying pathology (e.g., vitrectomy for macular traction detachment, cryo-retinopexy for retinal tear, scleral buckle for peripheral detachment, etc.), or
- visualization of the macula and a minimum of 180 degrees of the vitreous base allowed for a diagnosis that the underlying cause of the hemorrhage had been resolved without the need for further therapy and with documentation by a fundus photograph.

Any other outcome, including patients who discontinued prior to achieving treatment success and those who underwent a medically necessary intervention in the study eye prior to hemorrhage clearance (e.g., vitrectomy for diagnostic reasons), was considered a treatment non-success. Outcomes classified as non-successes were further classified as treatment failures or indeterminate outcomes. Treatment failures were patients who did not achieve the criteria for success and either remained in the study until at least the Month 3 visit or discontinued prior to the Month 3 visit due to an ocular adverse event in the study eye. Indeterminate described the patients who either discontinued prior to the Month 3 visit for any reason other than a SAE in the study eye without achieving success or who missed the Month 2 and Month 3 visits or the Month 3 visit without achieving success but who did not discontinue the study.

Safety Variable

The primary safety variable was the incidence of ocular adverse events following test agent injection reported during the study. In particular, the incidence of adverse events of no light perception, retinal detachment, iritis, hypopyon, ocular hyperemia, recurrent vitreous hemorrhage, eye pain, and visual acuity reduction were examined in detail. Secondary ocular safety variables were: changes in ocular symptoms, BCVA, IOP, lid examination, conjunctiva and cornea assessments, anterior chamber assessment, iris status, lens status, hemorrhage density, and the occurrence of interventions (e.g., cataract surgery and vitrectomy).

Secondary Efficacy Response Variables

Improvement in BCVA was the principal secondary efficacy response variable. Treatment success was defined as the first evidence of post-Vitrase BCVA improvement of at least three lines or $\geq$ 0.3 LogMAR units.

Other secondary efficacy endpoints included the following:

- achievement of success (as defined by BCVA improvement) by the Month 3 visit for all diabetics and stratified by diabetic type (non-diabetic, diabetic -Type I, and diabetic-Type II [non-insulin dependent])
- achievement of success as assessed by the investigator and recorded on the CRF
- incidents of vitrectomy by the Month 3 visit, stratified by BCVA improvement within three months post treatment
- reduction in hemorrhage density from baseline to the Month 3 visit post treatment

Hemorrhage density was measured on an ordinal grading scale of 0 to 4 in each of 12 clock hour segments of the eye. Entrance criteria required patients to have a grade of 3 or 4 in all 12 clock hours of the study eye. Two hemorrhage density response variables were analyzed, "Improvement" and "Marked Improvement." Improvement was a dichotomous response variable with possible values of "yes" (defined as 6 or more clock hours showing a grade of 0, 1, or 2 on or prior to the Month 3 visit) and "no" (otherwise). Marked Improvement was a dichotomous response variable with possible values of "yes" (defined as 6 or more clock hours showing a grade of 0 or 1 on or prior to the Month 3 visit) and "no" (otherwise).

Subject Disposition and Demographics

Table 5 - Subject Disposition (Saline Control Protocol) – Study VIT-02-08961X

Treatment	Number of Patients Screened and Randomized (N=750)	Number of Patients Discontinued (N=175)
Saline	193	39
7.5 IU Vitrase	181	42
55 IU Vitrase	179	38
75 IU Vitrase	197	56

Table 6 - Subject Disposition (Watchful Waiting Control Protocol) – Study VIT-02-08961X

Treatment	Number of Patients Screened and Randomized (N=71)	Number of Patients Discontinued (N=42)
Watchful waiting	18	14
7.5 IU Vitrase	18	11
55 IU Vitrase	18	8
75 IU Vitrase	17	6

Table 7
Discontinued Patients and Reason (Saline Control Protocol) – Study VIT-02-08961X

Patient	Treatment	Reason
126-2365	Saline	Death
138-2951	Saline	Death
149-3709	Saline	Death
151-3802	Saline	Death
168-4620	Saline	Death
171-4952	Saline	Death
112-1608	Saline	Did not qualify for study
104-2653	Saline	Lost to follow-up
107-1370	Saline	Lost to follow-up
112-1620	Saline	Lost to follow-up
120-2017	Saline	Lost to follow-up
126-2358	Saline	Lost to follow-up
126-2359	Saline	Lost to follow-up
135-2816	Saline	Lost to follow-up
146-3551	Saline	Lost to follow-up
149-3708	Saline	Lost to follow-up
163-9015	Saline	Lost to follow-up
165-9102	Saline	Lost to follow-up
165-9106	Saline	Lost to follow-up
165-9112	Saline	Lost to follow-up
170-5081	Saline	Lost to follow-up
162-4502	Saline	Misrandomized – hemorrhage not dense
107-1361	Saline	Non-compliance
128-2451	Saline	Patient withdrew consent
130-2552	Saline	Patient withdrew consent
130-2561	Saline	Patient withdrew consent
135-2820	Saline	Patient withdrew consent
135-2839	Saline	Patient withdrew consent
137-2902	Saline	Patient withdrew consent
139-3003	Saline	Patient withdrew consent
142-3301	Saline	Patient withdrew consent
147-3601	Saline	Patient withdrew consent
154-4004	Saline	Patient withdrew consent
164-9065	Saline	Patient withdrew consent
164-9075	Saline	Patient withdrew consent
170-5089	Saline	Patient withdrew consent
112-1612	Saline	Withdrew consent
112-1615	Saline	Withdrew consent
113-1658	Saline	Withdrew consent
168-4603	75IU	(serious adverse event) - cellulites
144-3451	75IU	(serious) adverse event – renal failure
137-2903	75IU	(serious) adverse event – tractional retinal detachment
101-1008	75IU	Death
109-1456	75IU	Death
109-1458	75IU	Death
130-2551	75IU	Death
130-2560	75IU	Death

Patient	Treatment	Reason
143-3351	75IU	Death
148-3652	75IU	Death
157-4151	75IU	Death
162-4503	75IU	Death
164-9059	75IU	Death
155-4054	75IU	Frail medical health
113-1654	75IU	HMO directed patient withdrawal
104-1221	75IU	Lost to follow-up
107-1366	75IU	Lost to follow-up
126-2357	75IU	Lost to follow-up
144-3453	75IU	Lost to follow-up
146-3555	75IU	Lost to follow-up
147-3602	75IU	Lost to follow-up
149-3702	75IU	Lost to follow-up
149-3705	75IU	Lost to follow-up
149-3713	75IU	Lost to follow-up
154-4001	75IU	Lost to follow-up
163-9002	75IU	Lost to follow-up
163-9009	75IU	Lost to follow-up
163-9012	75IU	Lost to follow-up
164-9078	75IU	Lost to follow-up
165-9113	75IU	Lost to follow-up
170-9295	75IU	Moved to Italy
120-2019	75IU	Non-compliance
120-2021	75IU	Non-compliance
112-1621	75IU	Patient bedridden
135-2822	75IU	Patient moved to Houston, TX
148-3651	75IU	Screen failure
134-2751	75IU	Transportation not available
174-4951	75IU	Travel difficulties/family heath problems
103-1103	75IU	Unable to continue to travel
168-4607	75IU	Vitreous hemorrhage clearing prior to injection
103-1155	75IU	Withdrew consent
104-1209	75IU	Withdrew consent
106-1304	75IU	Withdrew consent
109-1465	75IU	Withdrew consent
116-1812	75IU	Withdrew consent
120-2016	75IU	Withdrew consent
127-2403	75IU	Withdrew consent
131-2602	75IU	Withdrew consent
135-2823	75IU	Withdrew consent
135-2831	75IU	Withdrew consent
136-2851	75IU	Withdrew consent
139-3001	75IU	Withdrew consent
139-3004	75IU	Withdrew consent
157-4255	75IU	Withdrew consent
175-5122	75IU	Withdrew consent
180-5168	75IU	Withdrew consent
171-4804	7.5 IU	(serious) adverse event - ↑ IOP to 61mmHg (hx of POAG)
139-3005	7.5 IU	(serious) adverse event – hospitalized for kidney rejection
107-1362	7.5 IU	Death
122-2108	7.5 IU	Death

Patient	Treatment	Reason
145-3510	7.5 IU	Death
146-3553	7.5 IU	Death
165-9105	7.5 IU	Death
170-9301	7.5 IU	Death
181-0806	7.5 IU	Death
101-1006	7.5 IU	Did not meet entry criteria
106-1303	7.5 IU	Lost to follow-up
106-1306	7.5 IU	Lost to follow-up
109-1460	7.5 IU	Lost to follow-up
112-1619	7.5 IU	Lost to follow-up
126-2363	7.5 IU	Lost to follow-up
163-9013	7.5 IU	Lost to follow-up
163-9018	7.5 IU	Lost to follow-up
165-9104	7.5 IU	Lost to follow-up
170-5094	7.5 IU	Lost to follow-up
180-5166	7.5 IU	Lost to follow-up
135-2821	7.5 IU	Non-compliance
136-2852	7.5 IU	Non-compliance
149-3706	7.5 IU	Non-compliance
155-4052	7.5 IU	Patient in hospice care home
178-5141	7.5 IU	Patient in poor health/prolonged hospitalization
103-1101	7.5 IU	Patient withdrew consent
103-1157	7.5 IU	Patient withdrew consent
109-1459	7.5 IU	Patient withdrew consent
111-1555	7.5 IU	Patient withdrew consent
113-1652	7.5 IU	Patient withdrew consent
114-1706	7.5 IU	Patient withdrew consent
115-1752	7.5 IU	Patient withdrew consent
115-1753	7.5 IU	Patient withdrew consent
120-2025	7.5 IU	Patient withdrew consent
168-4613	7.5 IU	Vitreous hemorrhage clearing
145-3511	7.5 IU	Withdrew consent
163-9004	7.5 IU	Withdrew consent
164-9063	7.5 IU	Withdrew consent
170-990	7.5 IU	Withdrew consent
175-5129	7.5 IU	Withdrew consent
184-5061	7.5 IU	Withdrew consent
175-5121	7.5 IU	Withdrew consent – did not wand to participate any longer
175-5124	55IU	Withdrew consent
113-1653	55 IU	(serious) adverse event – recurrent VH (investigator misunderstood protocol and terminated patient)
146-3558	55 IU	(serious) adverse event – recurrent VH, underwent vitrectomy
107-1364	55 IU	Death
111-1554	55 IU	Death
112-1614	55 IU	Death
117-1851	55 IU	Death
155-4053	55 IU	Death
163-9008	55 IU	Death
172-0751	55 IU	Death
174-4956	55 IU	Death
180-5164	55 IU	Death
107-1373	55 IU	Did not meet entry criteria/B-scan show TRD

Patient	Treatment	Reason
144-3452	55 IU	Did not meet inclusion/exclusion criteria
129-2502	55 IU	Did not qualify
113-1655	55 IU	HMO directed patient withdrawal
146-3559	55 IU	Ineligible but already randomized
106-1305	55 IU	Lost to follow-up
135-2808	55 IU	Lost to follow-up
164-9061	55 IU	Lost to follow-up
167-9264	55 IU	Lost to follow-up
171-4803	55 IU	Lost to follow-up
172-4851	55 IU	Lost to follow-up
120-2023	55 IU	Non-compliance
135-2805	55 IU	Non-compliance
163-9019	55 IU	Non-compliance
107-1360	55 IU	Non-compliance/had vitrectomy elsewhere
109-1457	55 IU	Withdrew consent
109-1462	55 IU	Withdrew consent
1161815	55 IU	Withdrew consent
119-1952	55 IU	Withdrew consent
120-2027	55 IU	Withdrew consent
135-2817	55 IU	Withdrew consent
139-3002	55 IU	Withdrew consent
163-9021	55 IU	Withdrew consent
165-9103	55 IU	Withdrew consent
170-5088	55 IU	Withdrew consent
174-4955	55 IU	Withdrew consent
175-5130	55 IU	Withdrew consent
180-5175	55 IU	Withdrew consent

Demographics

Table 8 - Demographics (Intent-to-Treat) – Study VIT-02-08961X

		Watchful Waiting	Saline Control	7.5 IU Vitrase	55 IU Vitrase	75 IU Vitrase	P value
Age	Mean	66.2	62.9	60.7	61.3	62.3	0.3612(b)
	Std	9.3	12.7	13.3	12.5	12.9	
	Min	48	28	25	27	27	
	Max	81	93	97	90	90	
Age group							
18-30		0	1 (0.5%)	4 (2.2%)	2 (1.1%)	2 (1.0%)	
31-50		1 (5.6%)	25 (13%)	28 (15.5%)	30 (16.8%)	32 (16.2%)	
51-70		11 (61.1%)	112 (58.0%)	107 (59.1%)	103 (57.5%)	109 (55.3%)	
> 70		6 (33.3%)	54 (28.0%)	42 (23.2%)	43 (24%)	54 (27.4%)	
Sex							
Male		13 (72.2%)	101 (52.3%)	91 (50.3%)	83 (46.4%)	118 (59.9%)	0.0674(a)
Female		5 (27.8%)	92 (47.7%)	90 (49.7%)	95 (53.1%)	79 (40.1%)	
Race							
Caucasian		7 (38.9%)	99 (51.3%)	88 (48.6%)	89 (49.7%)	105 (53.3%)	0.7629(a)
Black		3 (16.7%)	12 (6.2%)	8 (4.4%)	8 (4.5%)	13 (6.6%)	
Asian		2 (11.1%)	9 (4.7%)	7 (3.9%)	7 (3.9%)	3 (1.5%)	
Other		6 (33.3%)	73 (37.8%)	78 (43.1%)	74 (41.3%)	76 (38.6%)	
Diabetic Status							
Non-diabetic		2 (11.1%)	38 (19.7%)	22 (12.2%)	36 (20.1%)	34 (17.3%)	0.2159(c)
Diabetic		16 (88.9%)	155 (80.3%)	159 (87.8%)	143 (79.9%)	163 (82.7%)	
Type 1		5 (31.3%)	76 (49.0%)	93 (58.5%)	73 (51%)	86 (52.8%)	
Type 2 (non-insulin dependent)		11 (68.8%)	79 (51.0%)	66 (41.5%)	70 (49.0%)	77 (47.2%)	

(a) chi-square test
(b) one-way ANOVA
(c) chi-square test (non-diabetic vs. type 1 vs. type 2)

Efficacy Analysis – Protocol VIT-02-08961X (intent-to-treat population)

♦Efficacy Variables

Table 9- Baseline Best Corrected Visual Acuity (BCVA) – VIT-02

	Saline Control (n=193)	7.5IU Vitrase (n=181)	55IU Vitrase (n=179)	75IU Vitrase (n=197)
Light Perception	29 (15.0%)	21 (11.6%)	23 (12.8%)	28 (14.2%)
Hand Motion	85 (44.0%)	88 (48.6%)	94 (52.5%)	91 (46.2%)
Count Fingers	50 (25.9%)	53 (29.3%)	42 (23.5%)	50 (25.4%)
Read Letters	27 (14.0%)	19 (10.5%)	19 (10.6%)	28 (14.2%)
Missing	2 (1.0%)	0	1 (0.6%)	0

P=0.8172 (Mantel-Haenszel chi-square test)

The majority of patients did not have a LogMAR score at study entry. In order to define a change in these patients that had vision that was off the chart, Light Perception, Hand Motion, and Count Fingers were used as "lines of vision". In addition, Read Letters (able to read at least one letter but less than five letters on the ETDRS chart at 1 meter) was accepted as a "line of vision". The difference between any two of these "lines" was equivalent to a 0.1 LogMAR change.

Patients were assigned a score of 1.6 LogMAR units if they were able to read at least one line (five letters) at one meter and a score of 1.7 LogMAR units if they could read between one and four letters. A score of 1.8, 1.9 and 2.0 LogMAR units was assigned to patients whose vision was recorded as Count Fingers, Hand Motion, or Light Perception, respectively.

Since patients had been recorded as having RL when a number of letters less than five had been read under varying conditions, a confirmatory analysis was conducted using the actual LogMAR score calculated for these patients. In other words, a LogMAR score was calculated based on any information given in the CRF concerning the number of letters read and the distance the patient was from the chart.

Table 10 - Cumulative Percentages of Patients Achieving a Three-line Improvement in BCVA (ITT population) – Study VIT-02-08961X

	Saline Control n=193	7.5IU Vitrase n=181	55 IU Vitrase n=179	75 IU Vitrase n=197	Overall p-value
Month 1[a]	34 (17.6%)	54 (29.8%) p=0.008	50 (27.9%) p=0.024	62 (31.5%) p=0.002	p= 0.0094
[CF = 1.8 LogMAR units, RL calculated][b]	35 (18.1%)	54 (29.8%) p=0.011	50 (27.9%) p=0.034	62 (31.5%) p=0.003	
Month 2	51 (26.4%)	61 (33.7%) p=0.155	70 (39.1%) p=0.012	79 (40.1%) p=0.006	p=0.0189
[CF = 1.8 LogMAR units, RL calculated]	52 (26.9%)	61 (33.7%) p=0.190	70 (39.1%) p=0.017	79 (40.1%) p=0.008	
Month 3	70 (36.3%)	67 (37.0%) p=0.966	78 (43.6%) p=0.183	89 (45 .2%) p=0.092	p=0.1843
[CF = 1.8 LogMAR units, RL calculated]	69 (35.8%)	67 (37.0%) p=0.883	78 (43.6%) p=0.151	89 (45.2%) p=0.073	

Data represents the number and percent of patients achieving BCVA improvement on or before the indicated visit (Month 1, Month 2 or Month 3). BCVA improvement is defined as the first evidence of post treatment change from baseline of at least three lines of vision or 0.3 LogMAR units.

The overall p-Value to compare treatment groups at each time point is based on the chi-square test. Pairwise comparisons of any dose of Vitrase to saline control are based on the two-tailed Z-test with no multiplicity adjustments.

[a] For the first analysis at each time point count fingers to any letters read is one line improvement. CF to 20/800 is a second line of improvement.

[b] For the confirmatory analysis at each time point Log MAR values greater than 1.6 (20/800) are not set to 1.7 Log MAR units but are calculated based on the information for distance and letters read collected on the CRF.

Table 11 - Cumulative Percentages of BCVA Improvement Stratified by Diabetic Type- Study VIT-02-08961X

	Diabetic Type n (Type I) / n (Type II)	Saline Control 76 / 79	7.5 IU Vitrase 93 / 66	55 IU Vitrase 73 / 70	75 IU Vitrase 86 / 77
Month 1	Type I	22.4%	37.6%	35.6%	32.6%
	Type II	12.7%	19.7%	30.0%	33.8%
Month 2	Type I	35.5%	39.8%	46.6%	39.5%
	Type II	21.5%	27.3%	42.9%	42.9%
Month 3	Type I	43.4%	44.1%	50.7%	47.7%
	Type II	32.9%	30.3%	45.7%	46.8%

Table 12- Watchful Waiting Control Protocol: Cumulative Percentage of BCVA Improvement – VIT-02-08961X

	Saline Control n=193	WWC n=18	7.5 IU Vitrase n=18	55 IU Vitrase n=19	75 IU Vitrase n=17
Month 1	34 (17.6%)	0	7 (38.9%)	5 (26.3%)	4 (23.5%)
Month 2	51 (26.4%)	1 (5.6%)	8 (44.4%)	6 (31.6%)	5 (29.4%)
Month 3	70 (36.3%)	2 (11.1%)	8 (44.4%)	6 (31.6%)	7 (41.2%)

Table 13- Surrogate Success Evaluation: Cumulative Incidence of Treatment "Success" on or Prior to Month 3 (ITT population) – VIT-02-08961X

	Saline Control n=193	7.5 IU Vitrase n=181	55 IU Vitrase n= 179	75 IU Vitrase n=197
Month 1	12 (6.2%)	23 (12.7%) p=0.048	27 (15.1%) p=0.009	28 (14.2%) p=0.015
Month 2	33 (17.1%)	46 (25.4%) p=0.065	56 (31.3%) p=0.002	55 (27.9%) p=0.015
Month 3	57 (29.5%)	57 (31.5%) p=0.765	68 (38.0%) p=0.106	70 (35.5%) p=0.248

Data represents the number and percent of patients achieving Surrogate Success on or before the indicated visit (Month 1, Month 2 or Month 3). **Patients were classified as a 'success' if the hemorrhage cleared sufficiently to facilitate the diagnosis of the underlying retinal pathology and to provide treatment, if necessary, of the underlying condition.** Patients were recorded as a treatment success dependent on completion of treatment, if necessary, or documentation that no further treatment was necessary. Pairwise comparisons are based on the two-tailed Z-test (Vitrase treatment versus saline control) with no multiplicity adjustments.

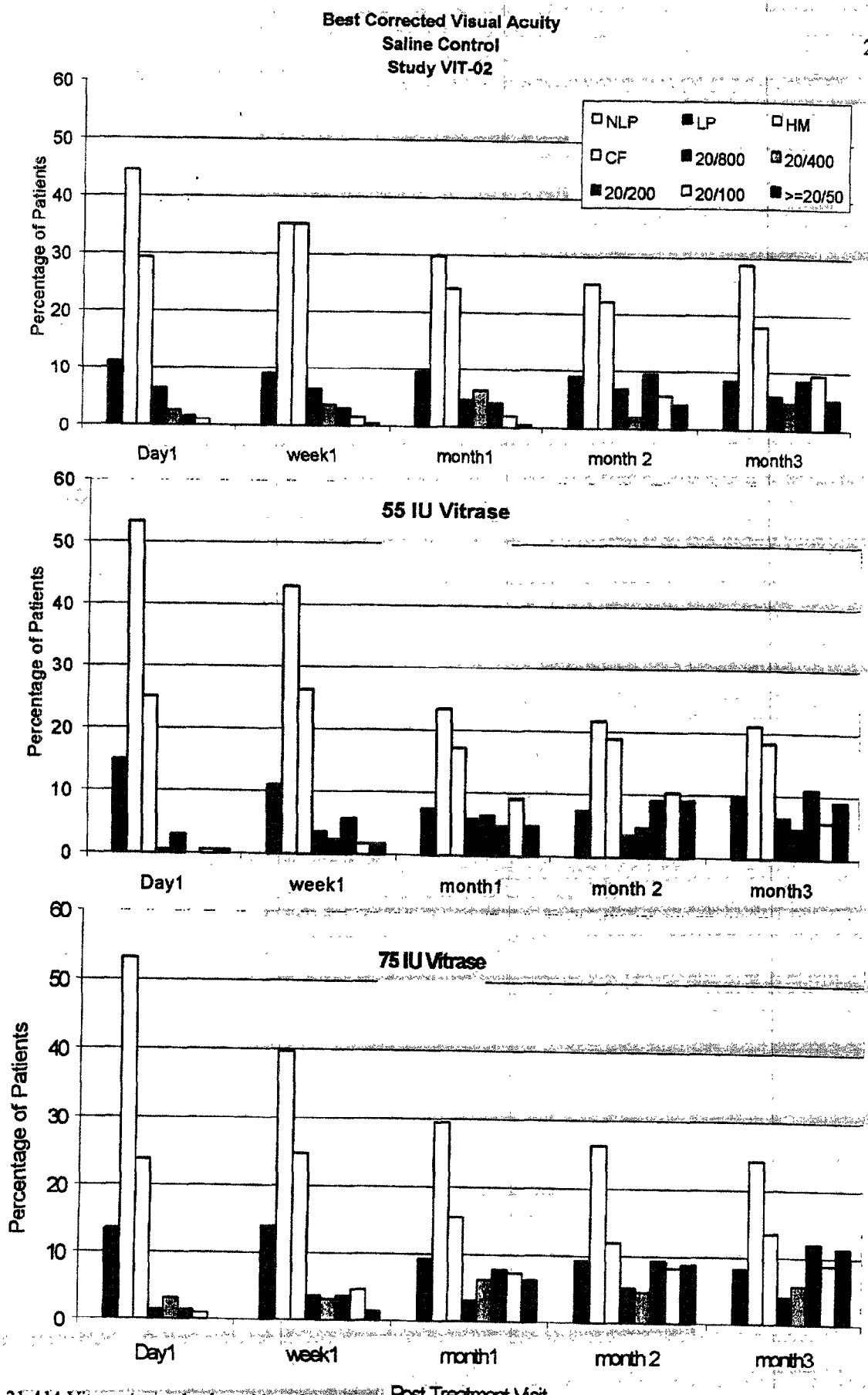
Best Corrected Visual Acuity
Saline Control
Study VIT-02
NLP
LP
HM
CF
20/800
20/400
20/200
20/100
>=20/50
Percentage of Patients
60
50
40
30
20
10
0
Day1
week1
month1
month 2
month3
55 IU Vitrase
75 IU Vitrase
Post Treatment Visit

Table 14- Cumulative Percentages with Reduction in Vitreous Hemorrhage Density (ITT population) – VIT-02-08961X

	Saline Control n=193	7.5 IU Vitrase n=181	55 IU Vitrase n=179	75 IU Vitrase n=197
Month 1	22 (11.4%)	45 (24.9%) p= 0.001	37 (20.7%) p=0.021	48 (24.4%) p=0.001
Month 2	45 (23.3%)	60 (33.1%) p=0.046	63 (35.2%) p= 0.016	71 (36.0%) p=0.008
Month 3	61 (31.6%)	65 (35.9%) p= 0.441	73 (40.8%) p= 0.083	84 (42.6%) p=0.032

Cumulative percentages of reduction of vitreous hemorrhage density were based on the following grading system:

Grade 0 - view of the retina/easily treatable
Grade 1 - retinal detail visible, some hemorrhage present but laser photocoagulation would still be possible
Grade 2 - large retinal vessels visible, central retinal detail is not visible enough to adequately place panretinal photocoagulation posterior to the equator
Grade3 - red reflex is visible but no central retinal detail is seen posterior to the equator
Grade 4 - no red reflex

An outcome of "reduced vitreous hemorrhage density" was determined using the following criteria: if the underlying condition was judged to be proliferative diabetic retinopathy (PDR) by the investigator, the hemorrhage density reduction was defined as at least six clock hours with density grades of 0 or 1 (which would allow for laser treatment in a minimum of six clock hours. Patients with branch retinal vein occlusion (BRVO) were required to have improvement in at least three clock hours with density grades of 0 or 1. p-values are based on the two-tailed z-test (Vitrase dose versus saline control) with no multiplicity adjustments.

Table 15- Cumulative Incidence of Vitrectomy at Each Posttreatment Visit – Study VIT-02-08961X

	Saline Control (n=193)	**7.5IU Vitrase (n=181)**	**55IU Vitrase (n=179)**	**75IU Vitrase (n=197)**
Vitrectomy on or prior to month 1	3 (1.6%)	7 (3.9%)	1 (0.6%)	2 (1.0%)
Vitrectomy on or prior to month 2	9 (4.7%)	12 (6.6%)	11 (6.1%)	7 (3.6%)
Vitrectomy on or prior to month 3	48 (24.9%)	50 (27.6%)	36 (20.1%)	46 (23.4%)

Adverse Events - Table 16
Number (%) of Patients with Ocular Adverse Events Reported by > 2% of Patients in Any Treatment Group in Study VIT-02-08961X

Preferred Term	Saline (N=191)	7.5 IU Vitrase (N=180)	55 IU Vitrase (N=175)	75 IU Vitrase (N=194)
Eye Disorder				
Iritis	90 (47.1%)	110 (61.1%)	134 (76.6%)	152 (78.4%)
Ocular Hyperemia	94 (49.2%)	101 (56.1%)	124 (70.9%)	131 (67.5%)
Eye Irritation	83 (43.5%)	95 (52.8%)	110(62.9%)	119 (62.9%)
Eye Pain	61 (31.9%)	63 (35%)	88 (50.3%)	98 (50.5%)
Lacrimation Increased	66 (34.6%)	56 (31.1%)	81 (46.3%)	94 (48.5%)
Visual Acuity Reduced	50 (26.2%)	70 (38.9%)	66 (37.7%)	73 (37.6%)
Vitreous Floaters	45 (23.6%)	55 (30.6%)	53 (30.3%)	67 (34.5%)
Photophobia	41 (21.5%)	52 (28.9%)	55 (31.4%)	67 (34.5%)
Vitreous Hemorrhage	41 (21.5%)	64 (35.6%)	54 (30.9%)	51 (26.3%)
Conjunctival Edema	39 (20.4%)	41 (22.8%)	53 (30.3%)	59 (30.4%)
Photopsia	15 (7.9%)	21 (11.7%)	34 (19.4%)	28 (14.4%)
Cataract Nuclear	24 (12.6%)	20 (11.1%)	21 (12%)	21 (10.8%)
Cataract subcapsular	15 (7.9%)	30 (16.7%)	17 (9.7%)	23 (11.9%)
Retinal Detachment	11 (5.8%)	19 (10.6%)	18 (10.3%)	23 (11.9%)
Cataract Cortical	16 (8.4%)	9 (5.0%)	19 (10.9%)	18 (9.3%)
Corneal Erosion	18 (9.4%)	10 (5.6%)	15 (8.6%)	14 (7.2%)
Conjunctival hemorrhage	18 (9.4%)	10 (5.6%)	13 (7.4%)	13 (6.7%)
Eyelid Edema	11 *5.8%)	9 (5.0%)	16 (9.1%)	17 (8.8%)
Corneal Edema	10 (5.2%)	14 (7.8%)	11 (6.3%)	16 (8.2%)
Eye discharge	10 (5.2%)	10 (5.6%)	15 (8.6%)	16 (8.2%)
Macular edema	10 (5.2%)	14 (7.8%)	6 (3.4%)	17 (8.8%)
Rubeosis Irides	11 (5.8%)	13 (7.2%)	10 (5.7%)	13 (6.7%)
Iris Adhesions	9 (4.7%)	4 (2.2%)	5 (2.9%)	15 (7.7%)
Erythema NEC	11 (5.8%)	7 (3.9%)	10 (5.7%)	14 (7.2%)
Corneal disorder NOS	7 (3.7%)	6 (3.3%)	5 (2.9%)	12 (6.2%)
Hyphema	5 (2.6%)	7 (3.9%)	5 (2.9%)	12 (6.2%)
Dry Eye NEC	5 (2.6%)	7 (3.9%)	5 (2.9%)	9 (4.6%)
Vision Blurred	5 (2.6%)	10 (5.6%)	4 (2.3%)	3 (1.5%)
Glaucoma NOS	5 (2.6%)	5 (2.8%)	1 (0.6%)	7 (3.6%)
Hypopyon	0	1 (0.6%)	3 (1.7%)	14 (7.2%)
Keratitis NEC	3 (1.6%)	4 (2.2%)	4 (2.3%)	7 (3.6%)
Maculopathy	5 (2.6%)	4 (2.2%)	3 (1.7%)	5 (2.6%)
Cataract NOS Aggravated	6 (3.1%)	4 (2.2%)	4 (2.3%)	4 (2.3%)
Blindness NEC	3 (1.6%)	5 (2.8%)	4 (2.3%)	3 (1.5%)
Cataract NEC	5 (2.6%)			
Vitreous Detachment	1 (0.5%)	3 (1.7%)	7 (4.0%)	3 (1.5%)
Post-Operative Pain	6 (3.1%)	0	1 (0.6%)	5 (2.6%)
Posterior Capsule Opacification	3 (1.6%)	1 (0.6%)	4 (2.3%)	4 (2.1%)
Intraocular Pressure Increased	1 (0.5%)	6 (3.3%)	2 (1.1%)	2 (1.0%)
Foreign Body Retained in Eye	1 (0.5%)	4 (2.2%)	2 (1.1%)	0
Infections and Infestations				
Nasopharyngitis	2 (1.0%)	4 (2.2%)	5 (2.9%)	5 (2.6%)

Pneumonia	5 (2.6%)	3 (1.7%)	6 (3.4%)	1 (0.5%)
Cellulitis	4 (2.1%)	0	3 (1.7%)	3 (1.5%)
Nervous System Disorders				
Headache	9 (4.7%)	12 (6.7%)	12 (6.9%)	14 (7.2%)
Cardiac Disorders				
Cardiac Failure Congestive	4 (2.1%)	4 (2.2%)	5 (2.9%)	5 (2.6%)
Cardiac Arrest	2 (1.0%)	1 (0.6%)	4 (2.3%)	2 (1.0%)
Gastrointestinal Disorders				
Nausea	6 (3.1%)	5 (2.8%)	10 (5.7%)	9 (4.6%)
Diarrhea	3 (1.6%)	3 (1.7%)	4 (2.3%)	2 (1.0%)
Metabolism and Nutrition Disorders				
Hypoglycemia	3 (1.6%)	0	2 (1.1%)	9 (4.6%)
Vascular Disorders				
Hypertension	2 (1.0%)	2 (1.1%)	7 (4.0%)	7 (3.6%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	3 (1.6%)	7 (3.9%)	4 (2.3%)	4 (2.1%)
Renal and Urinary Disorders				
Renal Failure	5 (2.6%)	2 (1.1%)	3 (1.7%)	4 (2/1%)
General Disorders and Administration Site Conditions				
Chest Pain	3 (1.6%)	4 (2.2%)	2 (1.1%)	4 (2.1%)
Psychiatric Disorders				
Anxiety	0	2 (1.1%)	3 (1.7%)	4 (2/1%)

Deaths

Forty (40) deaths were reported during the course of the study and one (1) death was reported approximately 400 days after a patient (Saline Control Protocol, 75 IU Vitrase) was discontinued from the study. Of the 41 deaths reported, 34 were in the Saline Control Protocol and 7 were in the Watchful Waiting Control Protocol.

The incidence was 3.1% (6/191) in the saline control group, and 3.9% (7/180), 5.7% (10/175), and 5.7% (11/194) in the 7.5 IU, 55 IU, and 75 IU Vitrase groups, respectively.

The majority of the deaths were cardiac-related. The causes of death included myocardial infarcts (4), cardiac arrest (11), end stage renal disease (2), sepsis/pneumonitis (3), cerebrovascular accident (4), complication of rectal surgery (1), cardiac failure (2), cerebral ischemia (1), aortic stenosis (1), myelodysplastic syndrome (1), disseminated intravascular vasculopathy (1), and "death" (3).

In the Watchful Waiting Control Protocol, 7 deaths were reported. Six (6) deaths were in the no treatment control group and 1 death was reported for the Vitrase groups. This patient was in the 7.5 IU treatment group and died as the result of a myocardial infarction. The causes of death in the control group were: myocardial infarction (3), cardiorespiratory arrest (1), hyperkalemia (1), and cardiovascular disease (1).

Study 2 - Protocol VIT-03-08961X

Title: Phase III Safety and Efficacy Study of Vitrase (ovine hyaluronidase) for Ophthalmic Intravitreous Injection for clearance of Severe Vitreous Hemorrhage

Objective: The primary objective of this study was to evaluate the safety and efficacy of a single intravitreous injection of 50ul of Vitrase (hyaluronidase), 55 IU, or 75 IU (equivalent to 68, and 93 USP units) compared with a single intravitreous injection of 0.9% sodium chloride injection USP (saline solution) for the treatment of vitreous hemorrhage.

Study Design: This was a three-arm, double-masked, prospective, randomized, parallel-group study. Patients were followed for a minimum of 12 months post-randomization and every six months thereafter. During the first 12 months, study visits were scheduled at 1 day, 1 week, and 1, 2, 3, 6, and 12 months post treatment.

Test Drug Schedule: Single intravitreous injection was administered in the study eye.

Table 17 - Clinical Sites – Study VIT-03-08961X

Site No.	Principal Investigator	Total Patients Randomized
AUSTRALIA		
329	Michael Branley, MD	3
333	William Campbell, MD	4
325	Andrew Chang, MD	1
335	Lawrence Lee, MD	3
337	Paul Mitchell, MD	5
336	Henry Newland, MD	1
BRAZIL		
351	Suel Abujamra, MD	24
339	Marcos Avila, MD	31
342	Michel Farah, MD	38
347	Jaco Lavinsky, MD	13
344	Carlos Augusto Moreira, Jr., MD	9
343	Marcio B. Nehemy, MD	2
HUNGARY		
355	Andras Berta, MD	1
338	George Deak, MD	18
341	Lajos Kolozsvari, MD	27
340	Balint Kovacs, MD	23
349	Tibor Milibak, MD	7
346	Gyorgy Salacz, MD	12
ITALY		
360	Emilio Balestrazzi, MD	5
356	Ugo Menchini, MD	7
354	Mario Stirpe, MD	2

Site No.	Principal Investigator	Total Patients Randomized
NETHERLANDS		
322	Marc D. de Smet, MD	3
320	Johanna Hooymans, MD	4
305	Robert Kuijpers, MD (formerly Eric van Oosterhout, MD)	2
POLAND		
334	Jozef Kaluzny, MD	25
327	Maria Kmera-Muszynska, MD	3
313	Jerzy Nawrocki, MD	39
301	Maria Hanna Nizankowska, MD	41
315	Krystyna Pecold, MD	7
302	Ryszard Philips, MD	8
348	Stefan Pojda, MD	20
345	Krystyna Raczynska, MD	20
304	Zbigniew Zagorski, MD	19
SOUTH AFRICA		
312	James Acton, MD	11
318	Christopher M. Johnston, MD	5
309	J. J. Krouse, MD	1
306	Louis Kruger, MD	7
321	Anne L. Peters, MD	17
310	Kelvin N. A. Rivett, MD	1
307	Jacobus S. Roelofse, MD	2
311	A. A. Stulting, MD	3
308	K. A. Woods, MD	1
SPAIN		
364	Francisco Clement-Fernandez, MD	3
363	Marta S. de Figueroa-Diez, MD	7
361	M^a Desamparados Navea-Tejerina, MD	5
362	Jose M^a Ruiz Moreno, MD	6
UNITED KINGDOM		
323	Hatem Atta, MD	14
326	Anthony G. Casswell, MD	6
324	Amresh Chopdar, MD	6
319	Cathryn Edrich, MD (formerly Dinesh Verma, MD)	10
352	R. H. B. Grey, MD	1
328	Carl Groenewald, MD	5
350	John D. A. McHugh, MD	6
353	Chong Sum Ng, MD	5
359	Paul Rosen, MD	6
332	Kevin Stannard, MD	4
317	Kenneth Swa, MD	1
358	Thomas H. Williamson, MD	3

Study Population – Inclusion and Exclusion Criteria
Same as Protocol VIT-02-08961X

Study Medications
Same as Protocol VIT-02-08961X

Study Masking
Same as Protocol VIT-02-08961X with the exception of the Watchful Waiting group masking. This protocol did not include a Watchful Waiting Control Group.

Efficacy Variable
Same as Protocol VIT-02-08961X

Safety Variable
Same as Protocol VIT-02-08961X

Study Design and Schedule of Assessments
Same as Protocol VIT-02-08961X

Subject Disposition and Demographics

Table 18- Subject Disposition (Saline Control Protocol) – Study VIT-03-08961X

Treatment	Number of Patients Screened and Randomized (N= 556)	Number of Patients Discontinued (N= 60)
Saline	190	22
55 IU Vitrase	186	18
75 IU Vitrase	180	20

Table 19 – Discontinued Patients and Reason Prior to Month 12 (Saline Control Protocol) – Study VIT-03-08961X

Patient	Treatment	Reason
301-6373	Saline	Death
301-6431	Saline	Death
310-8511	Saline	Death
313-6497	Saline	Death
319-5687	Saline	Death
319-5741	Saline	Death
321-8542	Saline	Death
340-5273	Saline	Death
346-5266	Saline	Death
351-8230	Saline	Death
306-8490	Saline	Lost to follow-up
321-8535	Saline	Lost to follow-up

Patient	Treatment	Reason
343-8106	Saline	Lost to follow-up
362-9630	Saline	Patient did not meet inclusion criteria
351-8173	Saline	Patient was not injected
304-6521	Saline	Patient withdrew consent
319-5692	Saline	Patient withdrew consent
324-5699	Saline	Patient withdrew consent
327-6404	Saline	Patient withdrew consent
329-7689	Saline	Patient withdrew consent
337-7719	Saline	Patient withdrew consent
347-8113	Saline	Patient withdrew consent
358-5771	Saline	Patient withdrew consent
342-8126	75 IU	(serious) adverse event – NLP vision
301-6361	75 IU	(serious) adverse experience – NLP vision
301-6528	75 IU	Death
312-8522	75 IU	Death
313-6384	75 IU	Death
313-6414	75 IU	Death
313-6496	75 IU	Death
319-5690	75 IU	Death
321-8539	75 IU	Death
326-5707	75 IU	Death
339-8138	75 IU	Death
347-8154	75 IU	Death
351-8119	75 IU	Death
313-6381	75 IU	Lost to follow-up
313-6398	75 IU	Lost to follow-up
342-8095	75 IU	Lost to follow-up
342-8168	75 IU	Lost to follow-up
319-5742	75 IU	Patient was not injected
301-6366	75 IU	Patient withdrew consent
324-5702	75 IU	Patient withdrew consent
328-5711	75 IU	Patient withdrew consent
301-6374	55 IU	Death
301-6427	55 IU	Death
313-6409	55 IU	Death
318-8529	55 IU	Death
321-8551	55 IU	Death
339-8212	55 IU	Death
351-8117	55 IU	Death
321-8540	55 IU	IOP to high for injection
311-8482	55 IU	Lost to follow-up
311-8483	55 IU	Lost to follow-up
344-8101	55 IU	Lost to follow-up
306-8489	55 IU	Non-compliance
350-5738	55 IU	Not eligible for injection
302-6367	55 IU	Patient withdrew consent
324-5700	55 IU	Patient withdrew consent
432-5701	55 IU	Patient withdrew consent
329-7687	55 IU	Patient withdrew consent
342-8189	55 IU	Vitrectomy performed in another service

Demographics

Table 20 - Demographics (Intent-to-Treat) – Study VIT-03-08961X

		Saline Control	55 IU Vitrase	75 IU Vitrase	P value
Age	Mean	61.1 (188)	61.7 (185)	62.9 (180)	0.366 (b)
	Std	12.6	11.9	12.0	
	Min	26	23	23	
	Max	93	87	91	
Age group					
18-30		3 (1.6%)	3 (1.6%)	2 (1.1%)	
31-50		26 (13.7%)	28 (15.1%)	23 (12.8%)	
51-70		118 (62.1%)	108 (58.1%)	105 (58.3%)	
> 70		41 (21.6%)	46 (24.7%)	50 (27.8%)	
Sex					
Male		84 (44.2%)	102 (54.8%)	93 (51.7%)	0.103 (a)
Female		106 (55.8%)	84 (45.2%)	86 (47.8%)	
Race					
Caucasian		160 (84.2%)	155 (83.3%)	152 (84.4%)	0.8475 (a)
Black		20 (10.5%)	16 (8.6%)	18 (10.0%)	
Asian		5 (2.6%)	8 (4.3%)	7 (3.9%)	
Other		5 (2.6%)	7 (3.8%)	3 (1.7%)	
Diabetic Status					
Non-diabetic		50 (26.3%)	66 (35.5%)	43 (23.9%)	0.09 (c)
Diabetic		140 (73.7%)	120 (64.5%)	137 (76.1%)	
Type 1		95 (67.9%)	88 (73.3%)	92 (67.2%)	
Type 2 (non-insulin dependent)		45 (32.1%)	32 (26.7%)	45 (32.8%)	

(a) chi-square test
(b) one-way ANOVA
(c) chi-square test (non-diabetic vs. type 1 vs. type 2)

Efficacy Analysis – Protocol VIT-03-08961X (intent-to-treat population)

♦Efficacy Variables

Table 21- Baseline Best Corrected Visual Acuity – Protocol VIT-03-08961X

	Saline Control n=190	55 IU Vitrase n=186	75 IU Vitrase n=180	Overall N=556
Light Perception	68 (35.8%)	61 (32.8%)	58 (32.2%)	187 (33.6%)
Hand Motion	87 (45.8%)	82 (44.1%)	89 (49.4%)	258 (46.4%)
Count Fingers	25 (13.2%)	31 (16.7%)	26 (14.4%)	82 (14.7%)
Read Letters	4 (2.1%)	11 (5.9%)	5 (2.8%)	20 (3.6%)
Missing or NA	6 (3.2%)	1 (0.5%)	2 (1.1%)	9 (1.6%)
p=0.2021				

Note:Baseline BCVA was collected at the screening visit. Baseline BCVA was missing for nine patients: 301-6454, 326-5709, 334-6449, 342-8123, 351-8142, 351-8143 (saline control); 356-9527 (55 IU); 344-8102, 313-6496 (75 IU). Two of these patients (351-8143, saline control and 356-9527, 55 IU) had an extra screening visit and BCVA from that visit was used for baseline BCVA assessment to determine BCVA improvement.

Table 22 - Cumulative Percentages of Patients Achieving a Three-line Improvement in BCVA – Protocol VIT-03-08961X

	Saline Control n=190	55 IU Vitrase n=186	75 IU Vitrase n=180	Overall p-value
Month 1	43 (22.6%)	62 (33.3%) p=0.028	43 (23.9%) p=0.870	p= 0.0383
Month 2	54 (28.4%)	80 (43.0%) p=0.004	65 (36.1%) p=0.141	p=0.0128
Month 3	62 (32.6%)	86 (46.2%) p=0.009	75 (41.7%) p=0.091	p=0.0234

Data represents the number and percent of patients achieving BCVA improvement on or before the indicated visit (Month 1, Month 2 or Month 3). BCVA improvement is defined as the first evidence of post treatment change from baseline of at least three lines of vision or 0.3 LogMAR units. Assessment of BCVA improvement was censored at the time of vitrectomy or recurrent vitreous hemorrhage in the study eye.

The overall p-Value to compare treatment groups at each time point is based on the chi-square test. Pairwise comparisons of any dose of Vitrase to saline control are based on the two-tailed Z-test with no multiplicity adjustments.

For the first analysis at each time point count fingers to any letters read is one line improvement. CF to 20/800 is a second line of improvement. For the confirmatory analysis at each time point Log MAR values greater than 1.6 (20/800) are not set to 1.7 Log MAR units but are calculated based on the information for distance and letters read collected on the CRF. There was no difference between these analyses for this trial.

Table 23- Cumulative Percentages of BCVA Improvement Stratified by Diabetic Type- Protocol VIT-03-08961

	Diabetic Type n (Type I) / n (Type II)	Saline Control 95 / 45	55 IU Vitrase 88 / 32	75 IU Vitrase 92 / 45
Month 1	Type I	22 (23.2%)	33 (37.5%)	17 (18.5%)
	Type II	7 (15.6%)	9 (28.1%)	15 (33.3%)
Month 2	Type I	31 (32.6%)	40 (45.5%)	29 (31.5%)
	Type II	7 (15.6%)	12 (37.5%)	21 (46.7%)
Month 3	Type I	33 (34.7%)	44 (50.0%)	35 (38.0%)
	Type II	11 (24.4%)	13 (40.6%)	21 (46.7%)

Best Corrected Visual Acuity
Saline Control

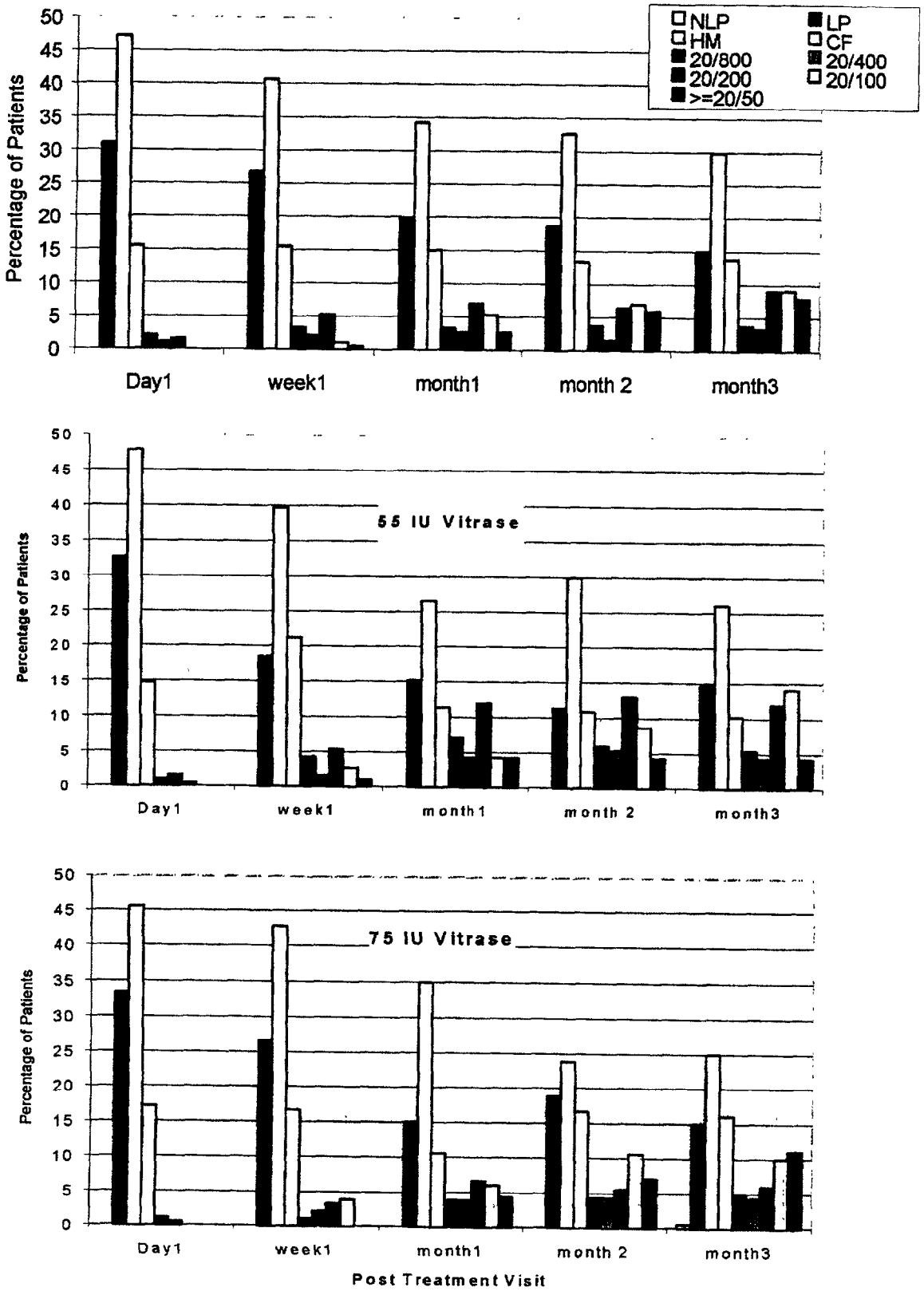

Table 24- Surrogate Success Evaluation: Cumulative Incidence of Treatment "Success" on or Prior to Month 3 – Protocol VIT-03-08961X

	Saline Control n=190	55 IU Vitrase n=186	75 IU Vitrase n=180
Month 1	9 (4.7%)	21 (11.3%) p=0.031	12 (6.7%) p=0.564
Month 2	29 (15.3%)	37 (19.9%) p=0.296	25 (13.9%) p=0.820
Month 3	41 (21.6%)	52 (28.0%) p=0.189	45 (25.0%) p=0.512

Data represents the number and percent of patients achieving Surrogate Success on or before the indicated visit (Month 1, Month 2 or Month 3). Patients were classified as a 'success' if the hemorrhage cleared sufficiently to facilitate the diagnosis of the underlying retinal pathology and to provide treatment, if necessary, of the underlying condition. Patients were recorded as a treatment success dependent on completion of treatment, if necessary, or documentation that no further treatment was necessary. Pairwise comparisons are based on the two-tailed Z-test (Vitrase treatment versus saline control) with no multiplicity adjustments.

Table 25- Cumulative Percentages of Reduction in Vitreous Hemorrhage Density – Protocol VIT-03-08961X

	Saline Control n=190	55 IU Vitrase n=186	75 IU Vitrase n=180
Month 1	20 (10.5%)	37 (19.9%) p=0.017	24 (13.3%) p=0.501
Month 2	37 (19.5%)	57 (30.6%) p= 0.017	43 (23.9%) p=0.366
Month 3	48 (25.3%)	68 (36.6%) p= 0.024	60 (33.3%) p=0.111

Table 26 - Cumulative Incidence of Vitrectomy at Each Posttreatment Visit – Study VIT-03-08961X

	Saline Control (n=190)	55IU Vitrase (n=186)	75IU Vitrase (n=180)
Vitrectomy on or prior to month 1	4 (2.1%)	3 (1.6%)	1 (0.6%)
Vitrectomy on or prior to month 2	8 (4.2%)	5 (2.7%)	4 (2.2%)
Vitrectomy on or prior to month 3	29 (15.3%)	21 (11.3%)	25 (13.9%)

Adverse Events

Table 27– Number (%) of Patients with Ocular Adverse Events Reported by > 2% of Patients in Any Treatment Group in Study VIT-03-08961X

Preferred Term	Saline (N=187)	55 IU Vitrase (N=184)	75 IU Vitrase (N=180)
Eye Disorders			
Iritis	36 (19.3%)	74 (40.2%)	78 (43.3%)
Ocular Hyperemia	46 (24.6%)	68 (37.0%)	71 (39.4%)
Eye Irritation	49 (26.2%)	43 (23.4%)	52 (28.9%)
Eye Pain	23 (12.3%)	41 (22.3%)	51 (28.3%)
Lacrimation Increased	21 (11.2%)	33 (17.9%)	35 (19.4%)
Vitreous Hemorrhage	25 (13.4%)	30 (16.3%)	31 (17.2%)
Conjunctival Edema	20 (10.7%)	33 (17.9%)	28 (15.6%)
Vitreous Floaters	22 (11.8%)	26 (14.1%)	24 (13.3%)
Photophobia	19 (10.2%)	24 (13.0%)	27 (15.0%)
Visual Acuity Reduced	24 (12.8%)	26 (14.1%)	17 (9.4%)
Retinal Detachment	15 (8.0%)	13 (7.1%)	18 (10.0%)
Cataract Cortical	11 (5.9%)	7 (3.8%)	11 (6.1%)
Cataract subcapsular	11 (5.9%)	6 (3.3%)	9 (5.0%)
Photopsia	7 (3.7%)	10 (5.4%)	9 (5.0%)
Cataract Nuclear	10 (5.3%)	8 (4.3%)	6 (3.3%)
Corneal Disorder NOS	1 (0.5%)	9 (4.9%)	12 (6.7%)
Iris Adhesions	4 (2.1%)	6 (3.3%)	12 (6.7%)
Eyelid Edema	4 (2.1%)	10 (5.4%)	7 (3.9%)
Eye discharge	8 (4.3%)	6 (3.3%)	4 (2.2%)
Rubeosis Irides	8 (4.3%)	5 (2.7%)	5 (2.8%)
Erythema NEC	4 (2.1%)	8 (4.3%)	4 (2.2%)
Cataract NEC	5 (2.7%)	6 (3.3%)	4 (2.2%)
Corneal Erosion	6 (3.2%)	7 (3.8%)	2 (1.1%)
Corneal Edema	2 (1.1%)	4 (2.2%)	8 (4.4%)
Conjunctival Hemorrhage	7 (3.7%)	1 (0.5%)	4 (2.2%)
Uveitis NOS	2 (1.1%)	5 (2.7%)	4 (2.2%)
Hypopyon	0	3 (1.6%)	6 (3.3%)
Glaucoma NOS	0	1 (0.5%)	5 (2.8%)
Macular edema	1 (0.5%)	3 (1.6%)	2 (1.1%)
Nervous System Disorder			
Headache	3 (1.6%)	4 (2.2%)	3 (1.7%)
Cerebral Vascular Accidents	3 (1.6%)	2 (1.1%)	4 (2.2%)
Vascular Disorders			
Hypertension	6 (3.2%)	3 (1.6%)	1 (0.6%)
Gastrointestinal Disorders			
Vomiting	4 (2.1%)	3 (1.6%)	1 (0.6%)
Constipation	4 (2.1%)	2 (1.1%)	1 (0.6%)

Deaths

There were a total of 28 (5%) deaths among the 551 patients included in the safety population for this trial. There were 10 deaths (5.4%) in the saline control group, 7 deaths (3.8%) in the 55 IU Vitrase group, and 11 deaths (6.1%) for the 75 IU Vitrase group.

In the saline control group, the majority of the ten deaths were related to cardiovascular conditions including myocardial infarct, embolus, and stroke. Other causes of death were non-Hodgkin's lymphoma and multi-system failure. In the 55IU Vitrase group, causes of death included cardiovascular disorders, stroke, hepatitis, hypoglycemic coma and pneumonia. In the 75 IU Vitrase group of 11 deaths, 6 were associated with cardiovascular disorders. Other causes of death included diabetic coma, acute pulmonary failure, acute renal failure and bronchial tumor.

VII. Integrated Safety Data

Table 28 – Number (%) of Patients with Adverse Events Reported by > 2% of Patients in Any Treatment Group in the Pooled Phase 3 Studies VIT-02-08961X and VIT-03-08961X

Preferred Term	WW (N=18)	Saline (N=378)	7.5 IU Vitrase (N=198)	55 IU Vitrase (N=377)	75 IU Vitrase (N=391)
Eye Disorders					
Iritis	4(22.2%)	128 (33.9%)	124 (62.6%)	223 (59.2%)	243 (62.1%)
Ocular Hyperemia	4 (22.2%)	142 (37.6%)	113 (57.1%)	204 (54.1%)	215 (55.0%)
Eye Irritation	10 (55.6%)	112 (29.6%)	90 (45.5%)	132 (35.0%)	141 (36.1%)
Eye Pain	3 (16.7%)	86 (22.8%)	74 (37.4%)	140 (37.1%)	164 (41.9%)
Lacrimation Increased	4 (22.2%)	87 (23.0%)	65 (32.8%)	124 (32.9%)	140 (35.8%)
Vitreous Hemorrhage	3 (16.7%)	99 (26.2%)	86 (43.4%)	111 (29.4%)	104 (26.6%)
Visual Acuity reduced	4 (22.2%)	76 (20/1%)	79 (39.9%)	105 (27.9%)	101 (25.8%)
Abnormal Sensation in eye	2 (11.1%)	68 (18.0%)	62 (31.3%)	101 (26.8%)	116 (29.7%)
Vitreous Floaters	6 (33.3%)	70 (18.5%)	65 (32.8%)	91 (24.1%)	101 (25.8%)
Photophobia	6 (33.3%)	61 (16.1%)	59 (29.8%)	87 (23.1%)	102 (26.1%)
Conjunctival Edema	1 (5.6%)	59 (15.6%)	48 (24.2%)	96 (25.5%)	89 (22.8%)
Retinal Detachment	3 (16.7%)	32 (8.5%)	24 (12.1%)	38 (10.1%)	47 (12.0%)
Cataract Nuclear	5 (27.8%)	36 (9.5%)	29 (14.6%)	37 (9.8%)	31 (7.9%)
Cataract subcapsular	2 (11.1%)	27 (7.1%)	34 (17.2%)	29 (7.7%)	39 (10.0%)
Photopsia	0	22 (5.8%)	23 (11.6%)	45 (11.9%)	38 (9.7%)
Cataract	5 (27.8%)	27 (7.1%)	14 (7.1%)	30 (8.0%)	31 (7.9%)

Preferred Term	WW (N=18)	Saline (N=378)	7.5 IU Vitrase (N=198)	55 IU Vitrase (N=377)	75 IU Vitrase (N=391)
Cortical					
Rubeosis Irides	1 (5.6%)	21 (5.6%)	17 (8.6%)	21 (5.6%)	24 (6.1%)
Corneal Edema	1 (5.6%)	12 (3.2%)	18 (9.1%)	22 (5.8%)	26 (6.6%)
Corneal Erosion	1 (5.6%)	24 (6.3%)	10 (5.1%)	25 (6.6%)	17 (4.3%)
Macular edema	1 (5.6%)	12 (3.2%)	22 (11.1%)	16 (4.2%)	24 (6.1%)
Conjunctival Hemorrhage	0	26 (6.9%)	12 (6.1%)	17 (4.5%)	18 (4.6%)
Eye discharge	0	18 (4.8%)	11 (5.6%)	23 (6.1%)	21 (5.4%)
Iris Adhesions	2 (11.1%)	14 (3.7%)	9 (4.5%)	13 (3.4%)	28 (7.2%)
Corneal disorder NOS	0	8 (2.1%)	6 (3.0%)	18 (4.8%)	26 (6.6%)
Hyphema	0	6 (1.6%)	9 (4.5%)	14 (3.7)	16 (4.1%)
Cataract NEC	0	12 (3.2%)	3 (1.5%)	11 (2.9%)	13 (3.3%)
Retinopathy Diabetic	1 (5.6%)	11 (2.9%)	7 (3.5%)	6 (1.6%)	14 (3.6%)
Blindness NEC	1 (5.6%)	6 (1.6%)	9 (4.5%)	7 (1.9%)	9 (2.3%)
Vision Blurred	0	8 (2.1%)	11 (5.6%)	7 (1.9%)	5 (1.3%)
Dry Eye NEC	0	7 (1.9%)	7 (3.5%)	5 (1.3%)	11 (2.8%)
Glaucoma NOS	0	6 (1.6%)	6 (3.0%)	6 (1.6%)	12 (3.1%)
Hypopyon	0	0	1 (0.5%)	6 (1.6%)	21 (5.4%)
Vitreous Detachment	1 (5.6%)	3 (0.8%)	4 (2.0%)	10 (2.7%)	7 (1.8%)
Cataract NOS aggravated	1 (5.6%)	8 (2.1%)	5 (2.5%)	5 (1.3%)	4 (1.0%)
Maculopathy	0	5 (1.3%)	6 (3.0%)	6 (1.6%)	6 (1.5%)
Retinal hemorrhage	0	7 (1.9%)	6 (3.0%)	6 (1.6%)	3 (0.8%)
Keratitis NEC	0	4 (1.1%)	4 (2.0%)	4 (1.1%)	8 (2.0%)
Intraocular Pressure Increased	0	3 (0/8%)	6 (3.0%)	3 (0.8%)	6 (1.5%)
Post-Operative Pain	1 (5.6%)	10 (2.6%)	0	2 (0.5%)	5 (1.3%)
Posterior Capsule Opacification	0	3 (0.8%)	2 (1.0%)	7 (1.9%)	5 (1.3%)
Uveitis NOS	1 (5.6%)	2 (0.5%)	2 (1.0%)	8 (2.1%)	4 (1.0%)
blepharitis	0	2 (0.5%)	4 (2.0%)	3 (0.8%)	7 (1.8%)
Corneal Epithelial Defect	1 (5.6%)	2 (0.5%)	3 (1.5%)	5 (1.3%)	2 (0.5%)
Skin and Subcutaneous Tissue					
Eyelid edema	0	15 (4.0%)	13 (6.6%)	29 (7.7%)	25 (6.4%)
Erythema NEC	0	16 (4.2%)	8 (4.0%)	21 (5.6%)	20 (5.1%)
Infections and Infestations					
Nasopharyngitis	0	3 (0.8%)	4 (2.0%)	5 (1.3%)	7 (1.8%)
Pneumonia NOS	0	5 (1.3%)	4 (2.0%)	6 (1.6%)	3 (0.8%)
Influenza	1 (5.6%)	3 (0.8%)	4 (2.0%)	4 (1.1%)	0
Nervous System Disorders					
Headache NOS	0	16 (4.2%)	12 (6.1%)	20 (5.3%)	23 (5.9%)
Cerebral	1 (5.6%)	4 (1.1%)	3 (1.5%)	5 (1.3%)	8 (2.0%)

Preferred Term	WW (N=18)	Saline (N=378)	7.5 IU Vitrase (N=198)	55 IU Vitrase (N=377)	75 IU Vitrase (N=391)
Vascular Accident NOS					
Cardiac Disorders					
Cardiac Failure Congestive	2 (11.1%)	5 (1.3%)	6 (3.0%)	6 (1.6%)	7 (1.8%)
Myocardial Infarction	3 (16.7%)	5 (1.3%)	5 (2.5%)	3 (0.8%)	9 (2.3%)
Gastrointestinal Disorders					
Nausea	1 (5.6%)	10 (2.6%)	5 (2.5%)	13 (3.4%)	11 (2.8%)
Vomiting NOS	1 (5.6%)	6 (1.6%)	2 (1.0%)	7 (1.9%)	4 (1.0%)
Diarrhea NOS	0	6 (1.6%)	3 (1.5%)	7 (1.9%)	3 (0.8%)
Metabolism and Nutrition Disorders					
Hypercholesterolemia	1 (5.6%)	5 (1.3%)	8 (4.0%	5 (1.3%)	5 (1.3%)
Hypoglycemia NOS	0	5 (1.3%)	0	2 (0.5%)	9 (2.3%)
Vascular Disorders					
Hypertension	0	9 (2.4%)	6 (3.0%)	13 (3.4%)	11 (2.8%)
Surgical and Medical Procedures					
Post-Operative Complications NOS	1 (5.6%)	10 (2.6%)	5 (2.5%)	8 (2.1%)	6 (1.5%)
Respiratory, Thoracic and Mediastinal Disorders					
dyspnea	2 (11.1%)	3 (0.8%)	7 (3.5%)	6 (1.6%)	4 (1.0%)
Renal and Urinary Disorders					
Renal Failure	1 (5.6%)	6 (1.6%)	4 (2.0%)	6 (1.6%)	6 (1.5%)
General Disorders and administration site conditions					
Chest Pain NEC	1 (5.6%)	5 (1.3%)	6 (3.0%)	2 (0.5%)	5 (1.3%)
Blood and Lymphatic System Disorder					
Anemia NOS	1 (5.6%)	4 (1.1%)	2 (1.0%)	12 (3.2%)	7 (1.8%)

Draft Advisory Committee Meeting Questions:

Are additional analyses of the data needed to understand the safety or efficacy of Vitrase for the treatment of vitreous hemorrhage?

Are additional studies needed to establish the efficacy of this product?

Has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage?

Is there a concern about the death rate observed in these studies?

What additional clinical studies would be helpful in further evaluating the potential benefits of Vitrase therapy?

Are there adverse experiences that are of particular concern for this product?

Does the committee recommend approval of Vitrase for the treatment of vitreous hemorrhage?